Infectious Causes of Stroke in Adults and Children: COVID-19 and Stroke

StrokeNet Webinar

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Outline

1. COVID-19
2. Epidemiology
3. Cardiovascular and cerebrovascular manifestations
4. Potential mechanisms
5. Collateral damage

COVID-19: The basics

- COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).
- Novel single-stranded enveloped RNA virus.
- Seventh known human coronavirus:
  - 4 common cold viruses: 229E, OC43, NL63, and HKU1
  - 3 severe acute respiratory syndrome (SARS): ARDS
    - SARS-CoV 2002: 10% case fatality
    - Middle East respiratory syndrome (MERS-CoV) 2012: 34% case fatality
    - Coronavirus disease 2019 (COVID-19): 1-3% case fatality

Clerkin KJ et al. Circulation 2020.

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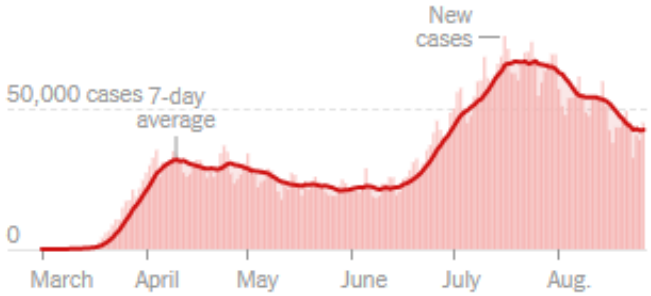
COVID-19 in the US

By The New York Times Updated August 27, 2020, 12:27 A.M. E.T.

Leer en español



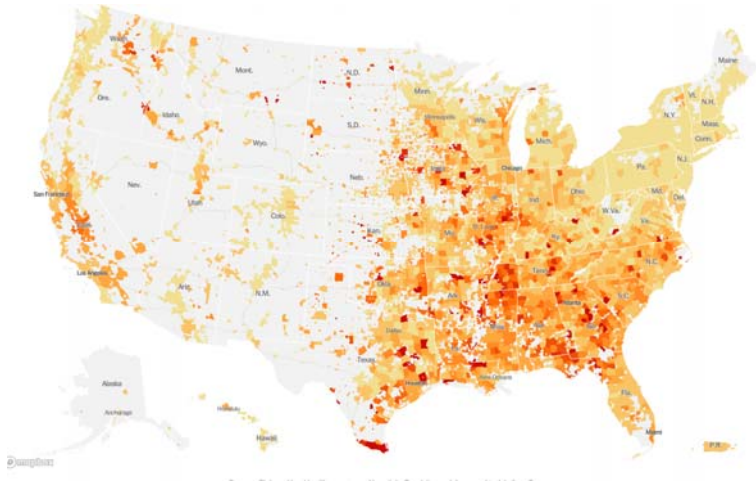
TOTAL CASES

5.8 million+

DEATHS

179,598

Includes confirmed and probable cases where available



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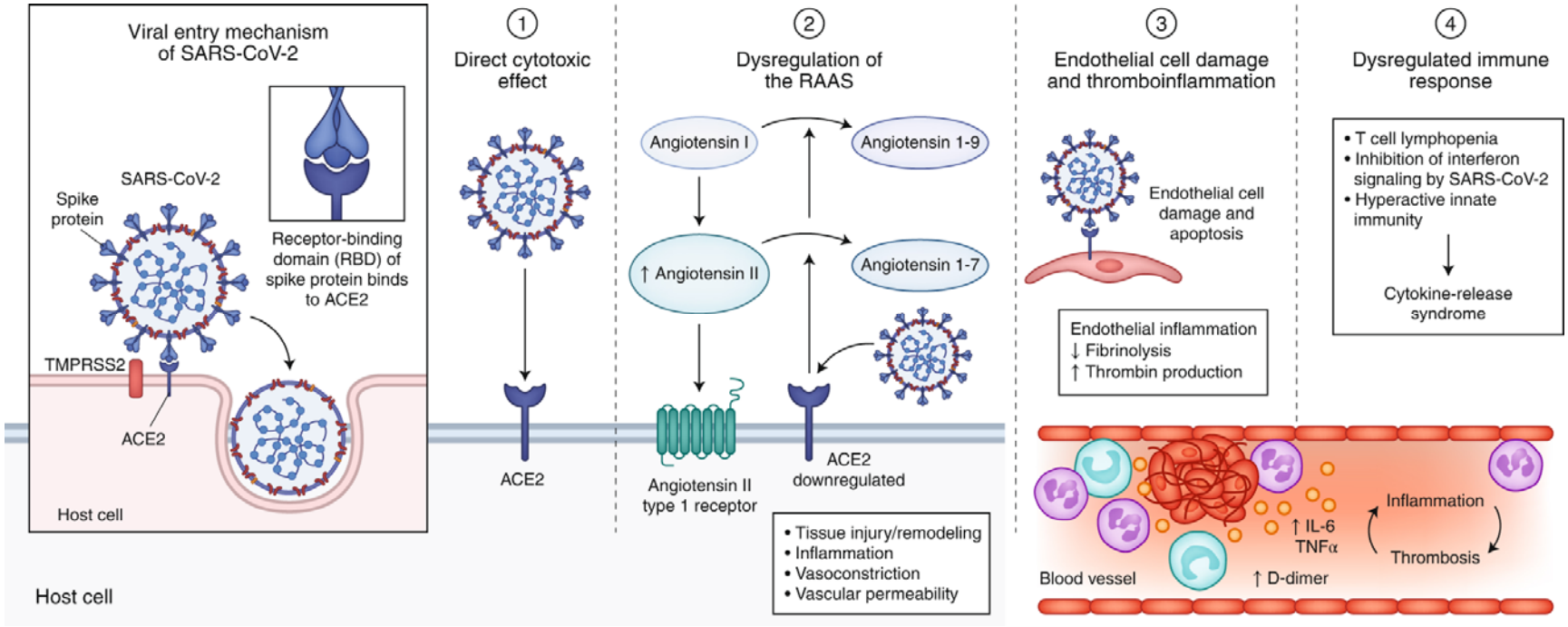
Pathophysiology of COVID 19



SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2 (far left). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the RAAS as a consequence of downregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; and (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα.

Gupta A et al. Nature Medicine 2020

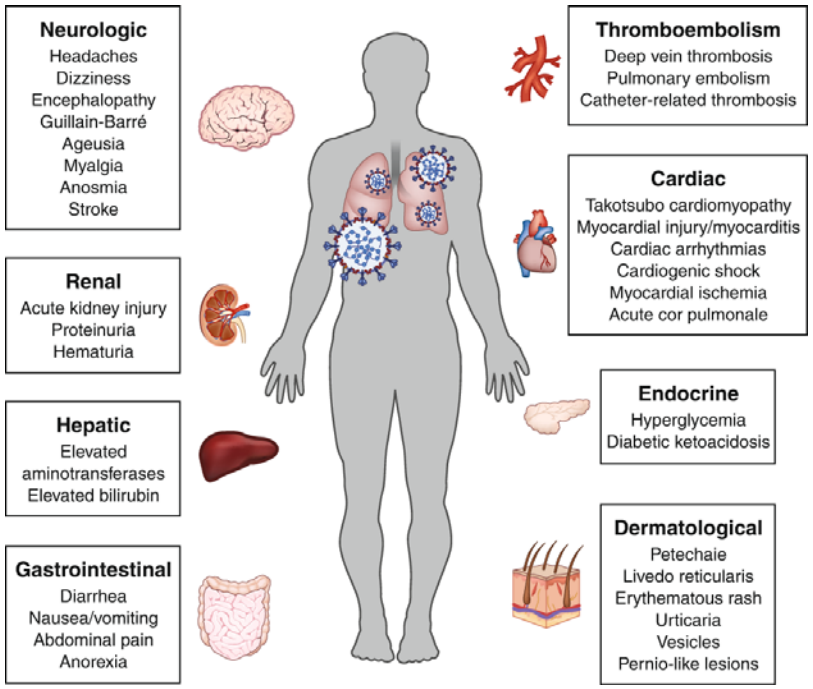
COVID-19 and cardiovascular disease/stroke

- Although COVID19 is primarily an infectious respiratory illness, it has cardiovascular relevance and consequent clinical implications.

  Clerkin KJ et al. Circulation 2020.
  Gupta A et al. Nature Medicine 2020.

- Some patients with COVID-19 *present* with primary cardiac complaints like chest pain and palpitations, *without fever*.

  Zheng YY et al. *Nat Rev Cardiol*. March 5, 2020.



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From: **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China**

JAMA. Published online February 07, 2020. doi:10.1001/jama.2020.1585

Table 4. Complications and Treatments of Patients Infected With 2019-nCoV

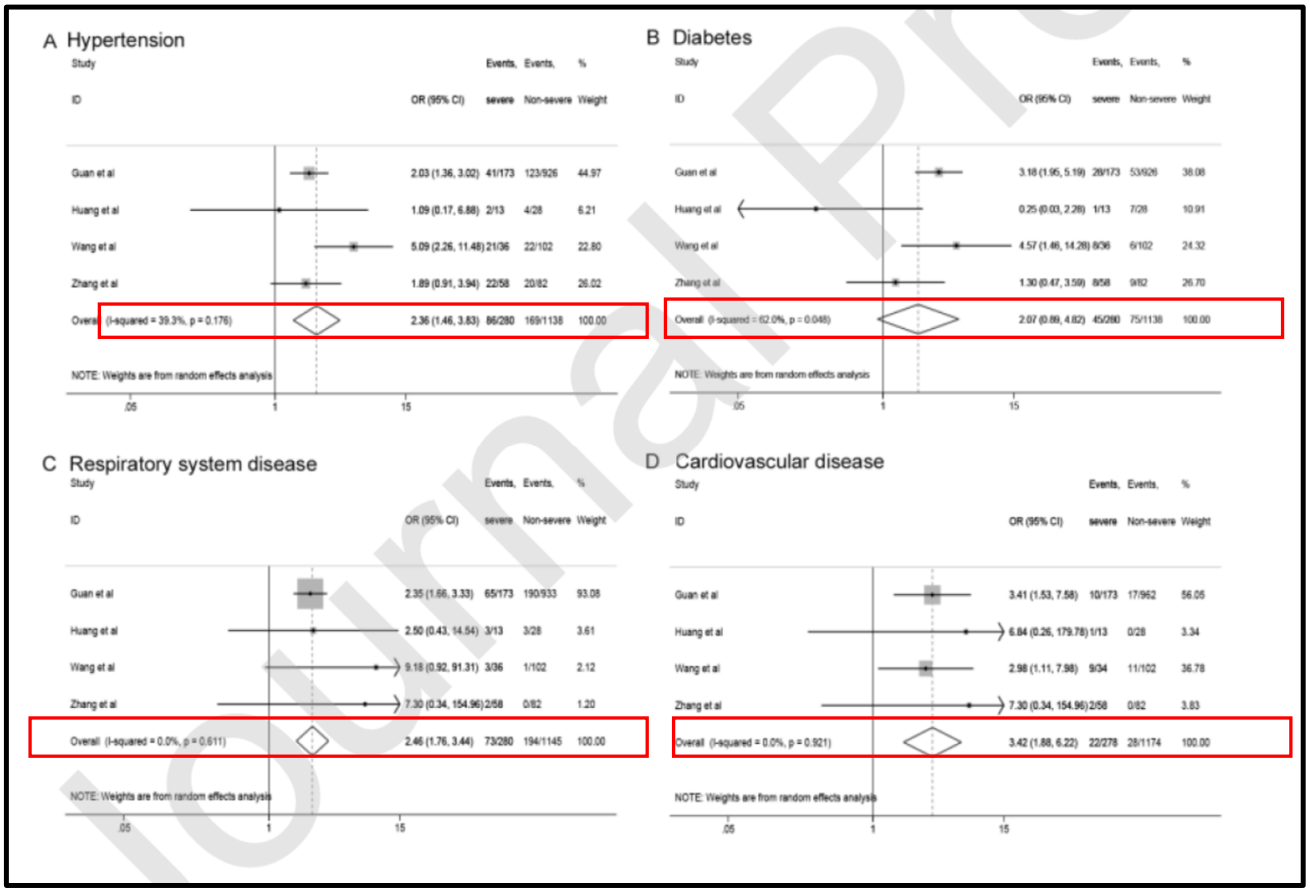
	No. (%)			
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	*P* Value[a]
Complications				
Shock	12 (8.7)	11 (30.6)	1 (1.0)	<.001
Acute cardiac injury	10 (7.2)	8 (22.2)	2 (2.0)	<.001
Arrhythmia	23 (16.7)	16 (44.4)	7 (6.9)	<.001
ARDS	27 (19.6)	22 (61.1)	5 (4.9)	<.001
AKI	5 (3.6)	3 (8.3)	2 (2.0)	.11
Treatment				
Antiviral therapy	124 (89.9)	34 (94.4)	90 (88.2)	.36
Glucocorticoid therapy	62 (44.9)	26 (72.2)	36 (35.3)	<.001
CKRT	2 (1.45)	2 (5.56)	0	>.99
Oxygen inhalation	106 (76.81)	4 (11.11)	102 (100)	<.001
NIV	15 (10.9)	15 (41.7)	0	<.001
IMV	17 (12.32)	17 (47.22)	0	<.001
ECMO	4 (2.9)	4 (11.1)	0	.004

Cardiovascular risk factors associated with worse outcomes

Meta-analysis of 8 studies
N=46,248
52% male; mean age 46 yrs

Hypertension	17%
DM	8%
Cardiovascular disease	5%
Respiratory disease	2%

Each was more common in those with severe disease than those with non-severe disease



Yang J et al. *Int J Infect Dis.* March 12, 2020.

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JAMA Network™

From: **Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China**

JAMA Neurol. 2020;77(6):683-690. doi:10.1001/jamaneurol.2020.1127

Table 1. Clinical Characteristics of Patients With COVID-19

Characteristic	No. (%) Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07
Skeletal muscle injury	23 (10.7)	17 (19.3)	6 (4.8)	<.001
Onset of symptoms to hospital admission, median (range), d				
CNS				
Dizziness	1 (1-30)	1 (1-30)	1 (1-14)	NA
Headache	1 (1-14)	1 (1-3)	3 (1-14)	NA
Impaired consciousness	8 (1-25)	10 (1-25)	1 (1-3)	NA
Acute cerebrovascular disease	9 (1-18)	10 (1-18)	1 (1)	NA
Ataxia	2 (2)	2 (2)	NA	NA
Seizure	2 (2)	2 (2)	NA	NA

Up to 3% overall incidence stroke

Increased (6%) in severely ill patients

Stroke in COVID-19

Table 1. Baseline characteristics of COVID-19 patients with new onset of CVD during infection

	Type of CVD	Subtype of AIS	Age, y	Sex	Smoking History	Drinking History	Blood pressure (mm Hg)	Fasting Blood-glucose (mmol/L)	Type of COVID-19 Patients (Severe/Non-Severe)	Onset Time of SARS-CoV-2 Infection	Onset Time of CVD	Treatment of CVD	Outcome Event
1	AIS	Small vessel	70	M	No	No	110/70	5·44	Severe	01/26/20	02/23/20	Antiplatelet	Survival
2	AIS	Large vessel stenosis	75	F	No	No	110/67	6 03	Severe	01/24/20	02/15/20	Antiplatelet	Survival
3	AIS	Cardioembolic	89	F	No	No	97/64	6·77	Non-severe	02/19/20	02/19/20	Anticoagulant	Survival
4	AIS	Large vessel stenosis	91	F	No	No	192/97	6·7	Severe	02/01/20	02/10/20	Anticoagulant	Survival
5	AIS	Large vessel stenosis	72	F	No	No	155/89	7·93	Severe	02/01/20	02/12/20	Anticoagulant	Survival
6	AIS	Cardioembolic	71	M	Yes	No	142/67	16·25	Severe	01/31/20	02/07/20	Anticoagulant	Death
7	AIS	Cardioembolic	86	M	Yes	No	110/72	13·81	Severe	01/24/20	02/11/20	Antiplatelet	Death
8	AIS	Large vessel stenosis	82	F	No	No	140/83	24·2	Severe	02/02/20	02/16/20	Antiplatelet	Death
9	AIS	Small vessel	78	M	Yes	No	156/82	11·0	Severe	01/17/20	01/17/20	Antiplatelet	Death
10	AIS	Large vessel stenosis	57	M	No	No	127/83	13·24	Non-severe	02/06/20	02/07/20	Antiplatelet	Survival
11	AIS	Small vessel	66	F	No	No	98/62	8·67	Severe	02/11/20	02/17/20	Anticoagulant	Survival
12	CVST		32	M	Yes	Yes	130/80	8·23	Severe	02/09/20	02/23/20	Anticoagulant	Survival
13	CH		62	M	Yes	Yes	150/80	5·81	Severe	01/23/20	02/01/20		Death

* The patients of COVID-19 were confirmed by SARS-CoV-2 RT-PCR positive in throat swab and viral-like pneumonia in chest CT.

Abbreviations: COVID-19, Coronavirus disease 2019; CVD, Cerebrovascular disease; AIS, Acute ischemia stroke; CH, Cerebral hemorrhage; CVST, Cerebral Venous Sinus Thrombosis; F, Female; M, Male

Li Y, et.al. Lancet. Mar 13 2020.

COVID-19 and cardiovascular disease/stroke

- Although COVID19 is primarily an infectious respiratory illness, it has cardiovascular relevance and consequent clinical implications.

  Clerkin KJ et al. Circulation 2020.

- Some patients with COVID-19 *present* with primary cardiac complaints like chest pain and palpitations, *without fever*.

  Zheng YY et al. *Nat Rev Cardiol*. March 5, 2020.

- Early reports in US suggest that some patients are presenting with stroke symptoms and then turn out to be COVID positive: related or simply reflection of high infection rate among asymptomatic people.

  Oxley T et al. NEJM 2020.

The Mount Sinai Experience

Table 1. Clinical Characteristics of Five Young Patients Presenting with Large-Vessel Stroke.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age — yr	33	37	39	44	49
Sex	Female	Male	Male	Male	Male
Medical history and risk factors for stroke†	None	None	Hyperlipidemia, hypertension	Undiagnosed diabetes	Mild stroke, diabetes
Medications	None	None	None	None	Aspirin (81 mg), atorvastatin (80 mg)
NIHSS score‡					
On admission	19	13	16	23	13
At 24 hr	17	11	4	19	11
At last follow-up	13 (on day 14)	5 (on day 10)	NA; intubated and sedated, with multiorgan failure	19 (on day 12)	7 (on day 4)
Outcome status	Discharged to rehabilitation facility	Discharged home	Intensive care unit	Stroke unit	Discharged to rehabilitation facility
Time to presentation — hr	28	16	8	2	8
Signs and symptoms of stroke	Hemiplegia on left side, facial droop, gaze preference, homonymous hemianopia, dysarthria, sensory deficit	Reduced level of consciousness, dysphasia, hemiplegia on right side, dysarthria, sensory deficit	Reduced level of consciousness, gaze preference to the right, left homonymous hemianopia, hemiplegia on left side, ataxia	Reduced level of consciousness, global dysphasia, hemiplegia on right side, gaze preference	Reduced level of consciousness, hemiplegia on left side, dysarthria, facial weakness
Vascular territory	Right internal carotid artery	Left middle cerebral artery	Right posterior cerebral artery	Left middle cerebral artery	Right middle cerebral artery
Imaging for diagnosis	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP, MRI	CT, CTA, MRI	CT, CTA, CTP
Treatment for stroke	Apixaban (5 mg twice daily)	Clot retrieval, apixaban (5 mg twice daily)	Clot retrieval, aspirin (81 mg daily)	Intravenous t-PA, clot retrieval, hemicraniectomy, aspirin (81 mg daily)	Clot retrieval, stent, aspirin (325 mg daily), clopidogrel (75 mg daily)
Covid-19 symptoms	Cough, headache, chills	No symptoms; recently exposed to family member with PCR-positive Covid-19	None	Lethargy	Fever, cough, lethargy
White-cell count — per mm^3	7800	9900	5500	9000	4900
Platelet count — per mm^3	427,000	299,000	135,000	372,000	255,000
Prothrombin time — sec	13.3	13.4	14.4	12.8	15.2
Activated partial-thromboplastin time — sec	25.0	42.7	27.7	26.9	37.0
Fibrinogen — mg/dl	501	370	739	443	531
D-dimer — ng/ml	460	52	2230	13,800	1750
Ferritin — ng/ml	7	136	1564	987	596

* Reference ranges are as follows: platelet count, 150,000 to 450,000 per cubic millimeter; prothrombin time, 12.3 to 14.9 seconds; activated partial-thromboplastin time, 25.4 to 34.9 seconds; fibrinogen, 175 to 450 mg per deciliter; D-dimer, 0 to 500 ng per milliliter; and ferritin, 30 to 400 ng per milliliter. CT denotes computed tomography, CTA CT angiography, CTP CT perfusion, MRI magnetic resonance imaging, NA not applicable, PCR polymerase chain reaction, and t-PA tissue plasminogen activator.
† The patients were screened for smoking, hypertension, hyperlipidemia, diabetes, atrial fibrillation, congestive heart failure, illicit drug use, and neck trauma.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher numbers indicating more severe stroke.

Oxley TJ, et al. *N Engl J Med*. 2020;382(20):e60.

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  Oxley T et al. NEJM 2020.

- Common infections, like influenza and sepsis, may **trigger** strokes and acute coronary events.

  Elkind MSV et al. Stroke. 2011;42:1851-1856.
  Boehme AK et al. Ann Clin Transl Neurol. 2018;5:456–463.

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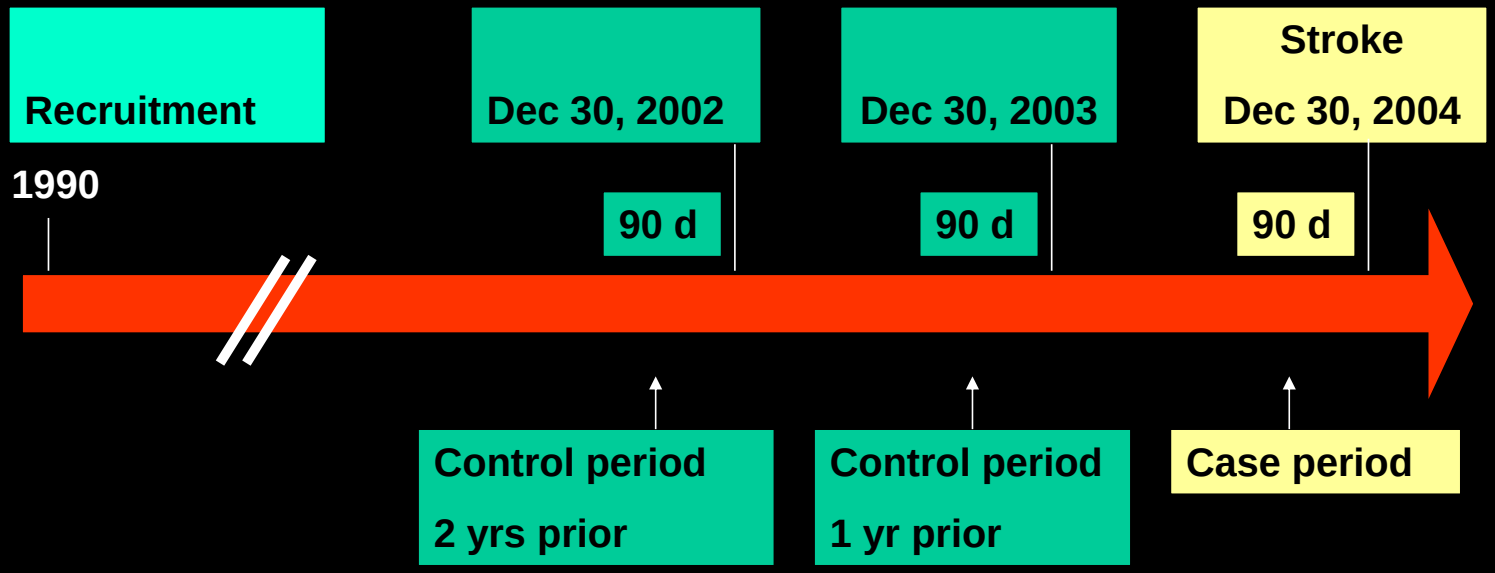
Cardiovascular Health Study
Case crossover design



Elkind MSV et al. Stroke 2011.

Results

Association of recent hospitalization for infection with ischemic stroke: Case-crossover analysis

Exposure-- Hosp for infection within:	Case intervals, n	Control intervals, n	OR	95 % CI
90 days prior to stroke				
No	631	1179		
Yes	29	17	3.4	1.8-6.5

Elkind MSV et al. Stroke 2011.

Results

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Exposure-- Hosp for infection within:	Case intervals, n	Control intervals, n	OR	95 % CI
90 days prior to stroke				
No	631	1179		
Yes	29	17	3.4	1.8-6.5
30 days prior to stroke				
No	655	1193		
Yes	11	3	7.3	1.9-40.9
14 days prior to stroke				
No	660	1194		
Yes	8	2	8.0	1.6-77.3

Elkind MSV et al. Stroke 2011.

HCUP/AHRQ California Case-Crossover Analysis: Influenza-like illness as a stroke trigger

Risk Window	OR	95% CI
15-DAY	6.5	2.2-19.7
30-DAY	3.7	1.8- 8.3
90-DAY	3.3	2.0- 5.8

Age Strata, 30-Day window

	OR	95% CI
<45 yrs	16.6	1.0- 267.2
45 to <=65 yrs	5.4	1.1- 27.5
>65 yrs	2.5	1.0-6.8

Boehme AK et al. Ann Clin Transl Neurol 2018;5(4):456-463.

Sepsis and risk of stroke: HCUP California State Inpatient Database

	Ischemic Stroke	Hemorrhagic Stoke
	OR (95% CI)	OR (95% CI)
Hospitalization for septicemia within 15 d before stroke	5.28 (3.65 - 7.64)	3.45 (2.04-5.84)
Hospitalization for septicemia within 30 d before stroke	4.58 (3.56-5.89)	3.74 (2.52 - 5.54)
Hospitalization for septicemia within 90 d before stroke	3.34 (2.85-3.91)	3.63 (2.77-4.76)
Hospitalization for septicemia within 180 d before stroke	3.14 (2.76-3.57)	3.62 (2.93- 4.48)

Interaction with age; p = 0.0006.

Stroke:
n=37,377 ischemic (n=3188 (8.5%) had sepsis within 180 days of stroke);
N=12,817 hemorrhagic (n=1101 (8.6%) had sepsis within 180 days of stroke)

Boehme AK et al. Stroke 2017;48:574-580.

Age-Adjusted Incidence Ratios of a Stroke during Risk Periods after Exposure to Vaccination or Infection

	Influenza Vaccination (N=4139)		Tetanus Vaccination (N=1355)		Pneumococcal Vaccination (N=1117)		Systemic Respiratory Tract Infection (N=6016)		Urinary Tract Infection (N=4273)	
Stroke	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
1–3 days	19	0.56 (0.35–0.89)	3	2.05 (0.66–6.41)	2	1.01 (0.25–4.04)	70	2.57 (2.03–3.27)	37	1.65 (1.19–2.28)
4–7 days	33	0.74 (0.52–1.05)	1	0.49 (0.07–3.52)	3	1.13 (0.36–3.52)	80	2.23 (1.78–2.80)	52	1.72 (1.31–2.28)
8–14 days	56	0.72 (0.55–0.94)	2	0.54 (0.13–2.20)	3	0.64 (0.21–2.00)	94	1.51 (1.23–1.86)	72	1.35 (1.06–1.72)
15–28 days	105	0.69 (0.57–0.85)	5	0.63 (0.26–1.55)	10	1.06 (0.57–2.00)	145	1.27 (1.07–1.50)	124	1.15 (0.96–1.39)
29–91 days	516	0.79 (0.71–0.87)	38	0.96 (0.67–1.37)	46	0.99 (0.72–1.35)	501	1.27 (1.15–1.41)	470	1.16 (1.04–1.29)
Baseline period	3396	1.00	1301	1.00	1053	1.00	4617	1.00	3472	1.00

* The numbers of participants exposed to each type of vaccination or infection are shown in parentheses for each exposure. These include a small number who had a recorded myocardial infarction or stroke on the day of exposure that was not included in the analysis, because the events may have been recorded retrospectively. Incidence during the baseline period served as the reference category. IR denotes age-adjusted incidence ratio, and CI confidence interval.

Smeeth, L. et al. N Engl J Med 2004;351:2611-2618

The NEW ENGLAND JOURNAL of MEDICINE

Many specific infections are associated with risks of specific stroke syndromes

Table 2. Selected Organisms Implicated in Stroke Pathogenesis

Organism	Infection	Postulated Mechanisms
Bacterial infections		
Treponema pallidum	Neurosyphilis	Arteritis, direct invasion of arterial wall, endotheliopathy
Chlamydia pneumoniae	Acute or chronic respiratory infections	Enhanced platelet aggregation, acceleration of atherosclerosis through induction of cytokines (tumor necrosis factor-alpha, interleukin 2) in response to specific antigenic stimulus, chronic inflammation due to multiple infections (infectious burden)
Helicobacter pylori	Gastritis, peptic ulcer disease	Enhanced platelet aggregation, prothrombotic state
Porphyromonas gingivalis (and other periodontal pathogens)	Periodontal disease	Chronic inflammation due to infectious burden; prothrombotic state
Parasitic infections		
Trypanosoma cruzi	Chagas disease, heart failure	Cardioembolism
Taenia solium	Neurocysticercosis	Arachnoiditis/small vessel arteritis; direct compression of large arteries by cysts
Plasmodium falciparum	Cerebral malaria	Occlusion of cerebral arteries by infected erythrocytes
Fungal infections		
Cryptococcus	Systemic and CNS infections (usually immunocompromises)	Meningitis; arteritis
Aspergillus	Systemic and CNS infections	Arteritis, infectious vasculopathy
Mucorales (including Rhizopus, Mucor, etc)	Mucormycosis	Vascular invasion of fungus with vascular necrosis, aneurysmal dilatation
Viral infections		
HIV	HIV disease/AIDS	Noninflammatory vasculopathy; susceptibility to opportunistic CNS infections, possible direct invasion of arterial wall, endotheliopathy
Cytomegalovirus	Often asymptomatic, latent; occasional mononucleosis-like syndrome	Inflammatory response with accelerated atherogenesis
Varicella-zoster virus	Chickenpox, shingles	Arteritis or noninflammatory vasculopathy, direct invasion of arterial wall, endotheliopathy
Herpes simplex virus (types 1 and 2)	Oral and genital infections	Noninflammatory vasculopathy; possible stroke trigger in young people, direct invasion of arterial wall, endotheliopathy, chronic inflammation due to infectious burden
Parvovirus B19	Fifth disease	Direct invasion of arterial wall, endotheliopathy
Influenza	Upper respiratory infection	Acute systemic infection as stroke trigger (platelet activation, dehydration, infection-induced cardiac arrhythmias)
SARS-CoV-2	COVID-19	Hypercoagulability, endotheliopathy, hyperinflammation, myocarditis, arrhythmia, complications of critical illness (renin-angiotensin system dysregulation, hypotension, hypoxemia)

CNS indicates central nervous system; COVID-19, coronavirus disease 2019; and SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Elkind et al. Stroke 2020 (In press).

Table 1. Characteristics of Patients with Covid-19, Stratified by the Diagnosis of Acute Ischemic Stroke

Characteristic[a]	Acute Ischemic Stroke (n=31)	No Acute Ischemic Stroke (n=2,101)
Demographics		
Age, years	69 (66-78)	62 (48-75)
Male sex	18 (58)	1,159 (55)
Race[b]		
White	9 (29)	602 (29)
Black	3 (10)	289 (14)
Asian	8 (26)	268 (13)
Other/Unknown	11 (35)	942 (45)
Hispanic ethnicity	1 (3)	397 (19)
Vascular Risk Factors		
Body mass index, kg/m^2	27 (24-31)	28 (23-33)
Hypertension	30 (97)	1,218 (58)
Diabetes	23 (74)	843 (40)
Hyperlipidemia	17 (55)	576 (27)
Atrial fibrillation	17 (55)	300 (14)
Chronic kidney disease	8 (26)	323 (15)
Coronary artery disease	16 (52)	492 (23)
COPD	4 (13)	190 (9)
Clinical Characteristics		
ICU admission	18 (58)	424 (20)
Mechanical ventilation	10 (32)	296 (14)
Prone positioning	9 (29)	222 (11)
Laboratory Data		
Initial D-dimer, ng/uL	1,930 (559-5,285)	682 (340-1,980)
Initial ESR, mm/hr	89 (60-106)	71 (45-99)
Initial WBC count, 10^3/uL	10.3 (6.9-12.9)	6.9 (5.0-9.6)
Initial platelet count, 10^3/uL	210 (178-269)	208 (161-274)
Initial troponin-I, ng/mL	0.03 (0.03-0.09)	0.03 (0.03-0.06)

The Weill-Cornell Experience

From March 4-May 2020 (2 months):
N= 2132 patients with COVID-19 (PCR positive)
n= 31 (1.5%) with ischemic stroke (95% CI 1.0-2.1%)

Compared to influenza (2016-2018)
N=1516 cases influenza
n= 3 (0.2%) with ischemic strokes

Adjusted OR for stroke with COVID-19 = 7.5
(95%CI 2.3-24.9%)

Merkler AE et al. Risk of Ischemic Stroke in Patients with COVID-19 versus in Patients with Influenza. JAMA Neurology 2020.

The Weill-Cornell Experience

Table 2. Characteristics of Acute Ischemic Stroke Among Patients with Covid-19	
Characteristic[a]	**Acute Ischemic Stroke** (n=31)
Stroke symptoms were presenting complaint	8 (26)
NIH Stroke Scale (IQR)	16 (6-23)
Stroke mechanism[b,c]	
Cardioembolic	13 (42)
Large-artery atherosclerosis	2 (7)
Small vessel disease	0 (0)
Other determined	0 (0)
Cryptogenic	16 (52)
ESUS	5(16)
Multiple causes	3 (10)
Incomplete evaluation	8 (26)
Multiple cerebrovascular territories involved	17 (55)
Antiplatelet use prior to stroke	7 (23)
Anticoagulant use prior to stroke	4 (13)
Intravenous thrombolysis administered	3 (10)
Mechanical thrombectomy performed	2 (7)
Symptomatic hemorrhagic transformation	2 (7)

Abbreviations: IQR, interquartile range; ESUS, embolic stroke of undetermined source

[a]Data reported as number (%) unless otherwise specified.

[b]According to the Trial of Org 10172 Acute Stroke Treatment (TOAST) criteria and the Embolic Stroke of Undetermined Source (ESUS) classification.

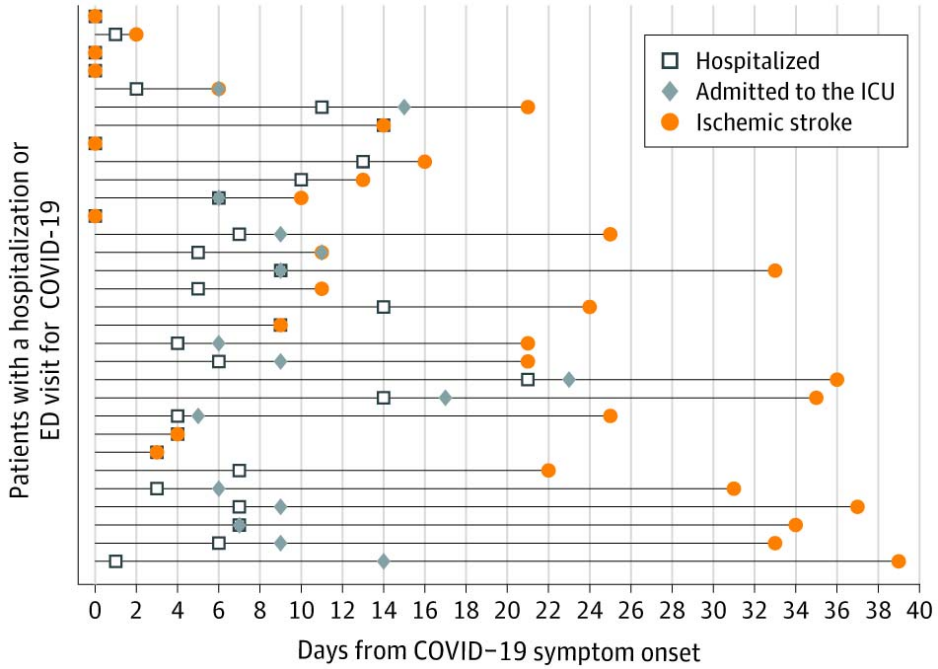
[c]Percentages were rounded up and therefore many not add to 100%.

26% presented with stroke
Median NIHSS 16
>50% cryptogenic/cardioembolic
26% incomplete evaluation

Merkler AE et al. Risk of Ischemic Stroke in Patients with COVID-19 versus in Patients with Influenza. JAMA Neurology 2020.

From: **Risk of Ischemic Stroke in Patients With Coronavirus Disease 2019 (COVID-19) vs Patients With Influenza**

JAMA Neurol. Published online July 02, 2020. doi:10.1001/jamaneurol.2020.2730



Timeline in Days From Coronavirus Disease 2019 (COVID-19) Symptom Onset to Acute Ischemic Stroke DiagnosisHorizontal lines represent individual patients with a hospitalization or emergency department (ED) visit for COVID-19 infection who had acute ischemic stroke. A white square indicates the day of hospitalization, a gray diamond indicates the day of intensive care unit (ICU) admission, if applicable, and an orange circle indicates the day of acute ischemic stroke diagnosis. For patients who did not have preceding typical COVID-19 symptoms, the day of their stroke was considered the day of COVID-19 symptom onset. For patients with typical symptoms of COVID-19 but without a clear onset date, the date of hospital presentation was considered the day of onset.

Table 2. Demographic and Clinical Characteristics of Patients With COVID-19 and Stroke Versus Contemporary and Historical Ischemic Stroke Controls

	COVID-19 Positive (A) (n=32)	COVID-19 Negative (B)* (n=46)	Historical Controls (C) (n=80)	*P* Value (A vs B)	*P* Value (A vs C)	*P* Value (B vs C)
Age, median (IQR)	63 (17)	70 (18)	68.5 (23)	0.001	0.078	0.881
Sex (% men)	71.9% (23)	52.2% (24)	45.0% (36)	0.102	0.012	0.464
Hypertension (%)	56.3% (18)	76.1% (35)	80.0% (64)	0.086	0.017	0.655
Diabetes mellitus (%)	34.4% (11)	28.3% (13)	30.0% (24)	0.623	0.658	1.000
Hyperlipidemia (%)	56.3% (18)	50.0% (23)	42.5% (34)	0.649	0.213	0.460
Congestive heart failure (%)	6.3% (2)	10.9% (5)	5.0% (4)	0.694	1.000	0.285
Coronary artery disease (%)	15.6% (5)	26.1% (12)	20.0% (16)	0.404	0.790	0.506
Atrial fibrillation (%)	18.8% (6)	21.7% (10)	25.0% (20)	0.784	0.622	0.829
History of stroke or TIA (%)	3.1% (1)	13.0% (6)	25.0% (20)	0.230	0.007	0.169
Active smoking (%)	0% (0)	4.3% (2)	12.8% (10/78)	0.513	0.059	0.207
NIHSS score, median (IQR)	19 (23)	8 (12)	3 (12)	0.007	0.001	0.071
D-dimer level (ng/mL) closest to stroke diagnosis, median (IQR)	3913 (7451)	526 (2752)	NA	0.023	NA	NA
Highest D-dimer (ng/mL) level during hospitalization, median (IQR)	>10,000 (7427)	525 (2871)	NA	0.011	NA	NA
CRP level, median (IQR), ng/mL	101.1 (175.5)	37.2 (130.7)	NA	0.208	NA	NA
ESR level, median (IQR)	79 (53)	40 (86)	41 (52)	0.172	0.001	0.860
Troponin level ≥0.1 mg/dL	45.2% (14/31)	23.1% (9/39)	8.1% (6/74)	0.073	<0.001	0.039
Large vessel occlusion (%)	45.5% (10/22)	27.9% (12/43)	20.3% (16/79)	0.318	0.026	0.372
Alteplase (%)	12.5% (4)	10.9% (5)	7.5% (6)	1.000	0.468	0.528
Thrombectomy (%)	18.8% (6)	17.4% (8)	13.8% (11)	1.000	0.563	0.612
Anticoagulation (%)	78.1% (25)	23.9% (11)	25.0% (20)	<0.001	<0.001	1.000
Stroke subtype				0.011	0.001	0.365
Cardioembolic	21.9% (7)	21.7% (10)	35.0% (28)			
Large vessel disease	6.3% (2)	17.4% (8)	21.3% (17)			
Small vessel disease	0% (0)	13.0% (6)	10.0% (8)			
Cryptogenic	65.6% (21)	30.4% (14)	25.0% (20)			
Other defined mechanisms	6.3% (2)	17.4% (8)	8.8% (7)			
Cryptogenic stroke (vs other mechanism) (%)	65.6% (21)	30.4% (14)	25.0% (20)	0.003	<0.001	0.537
Embolic stroke of undetermined source (vs other mechanism)* (%)	50.0% (11/22)	25.0% (11/44)	24.1% (19/79)	0.055	0.033	1.000
In-hospital death (%)	63.6% (14/22)	9.3% (4/43)	6.3% (5)	<0.001	<0.001	0.718

COVID-19 indicates coronavirus disease 2019; CRP, C-reactive protein measured in ng/mL; ESR, erythrocyte sedimentation rate measure in mm/h; IQR, interquartile range; NA, not available; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Patients with incomplete diagnostic evaluation were excluded, +one patient with cryptogenic stroke excluded due to upper respiratory in the week before admission but no COVID testing performed.

The NYU Experience

N= 3556 hospitalized patients with COVID-19
n= 32 ischemic strokes (0.9%)

66% cryptogenic
Elevated D-dimer and inflammatory levels
NIHSS median 19
64% mortality

Yaghi S, et al. *Stroke*. 2020.

Columbia University Irving Medical Center Experience

	COVID+ Stroke (N=58)	COVID- Stroke (N=117)
Age, median (range)	66 (34-94)	66 (35-101)
NIHSS on admission, median (range)	17 (1-38)	9 (0-40)
Race-ethnicity		
Black	8 (17.8%)	20 (21.2%)
Hispanic	24 (53.3%)	40 (42.1%)
Non-Hispanic white	13 (28.9%)	35 (36.8%)
HTN	37 (63.8%)	88 (75.2%)
DM	20 (34.5%)	46 (39.3%)
Afib	8 (13.8%)	29 (24.8%)
CHF	4 (6.9%)	5 (4.3%)
DVT	1 (1.7%)	5 (4.3%)
HLD	20 (34.5%)	48 (41.0%)
Smoker	2 (3.5%)	18 (15.4%)
CVD	12 (20.7%)	30 (25.6%)
CKD	10 (17.2%)	24 (20.5%)
Liver Disease	3 (5.1%)	2 (1.7%)
History of Cancer	6 (10.3%)	18 (15.4%)
History of Substance Abuse	1 (1.7%)	7 (5.9%)
History of MI	10 (17.2%)	13 (11.1%)
History of Stroke	14 (24.1%)	26 (22.2%)
HF	6 (10.3%)	8 (6.8%)
Immune Disorders	5 (8.6%)	3 (2.6%)
Pulmonary Disease	7 (12.1%)	11 (9.4%)
History of ILI symptoms in the past 45 days	38 (82.6%)	43 (39.5%)

N= 5,906 patients positive COVID-19 diagnosis
n= 56 (0.95%) stroke

Of 175 stroke patients Feb 1- May 19, 2020:
58 (33%) diagnosed with COVID
52 diagnosed at time of stroke
6 diagnosed prior to stroke admission

Stroke types:
31 (53.5%) ischemic
59% cardioembolic
21% ESUS
20% athero/small vessel
9 (15.5%) ICH
4 (6.9%) SAH
14 (24%) unknown

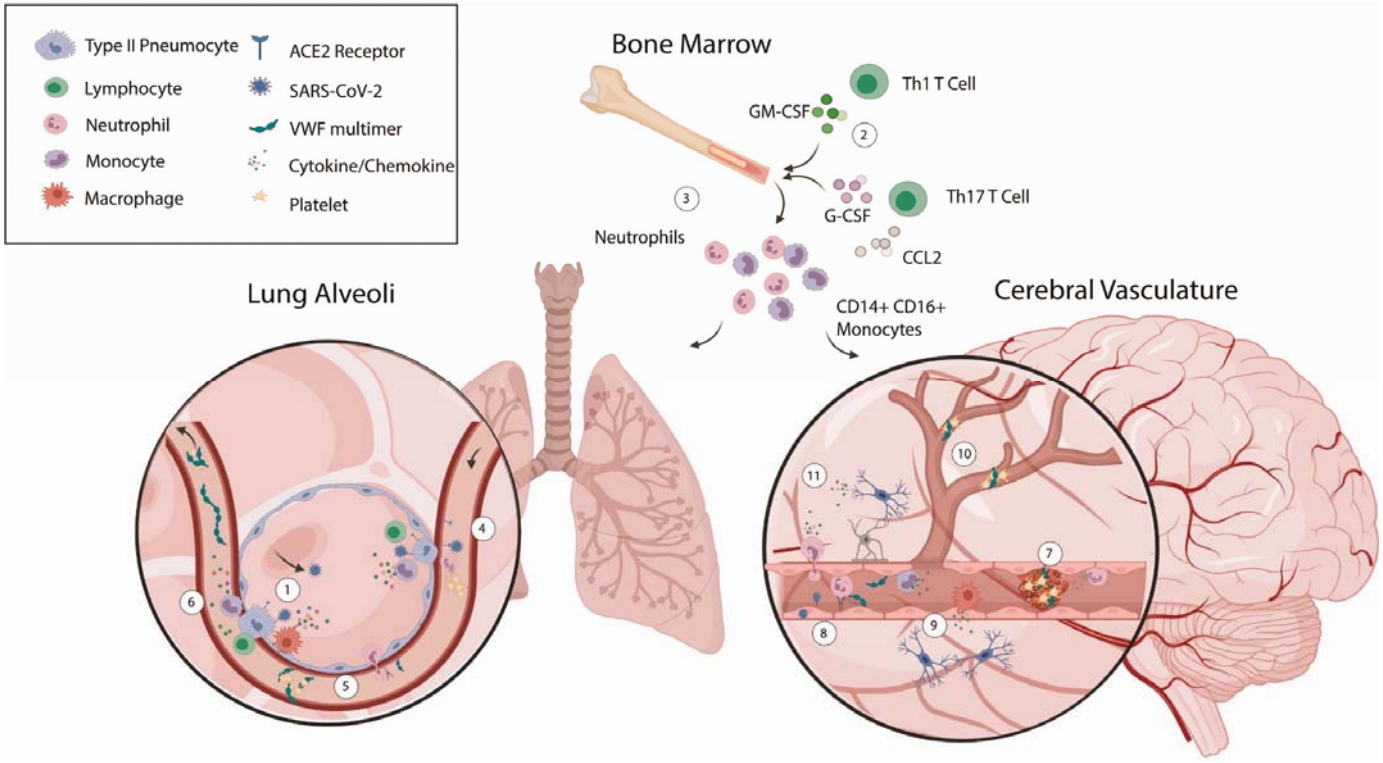
Boehme AK. Unpublished data

COVID-19 and CVD/stroke

Potential mechanisms

- Increased number of risk factors or comorbid conditions with age
- Cardiac events (arrhythmia/heart failure)
- Hypercoagulability and thrombosis
  - Antiphospholipid antibodies
- Hyperinflammation/"cytokine storm"/"Thromboinflammation"
- Complement activation/microangiopathy/endotheliitis
- Renin-angiotensin system dysregulation
- Direct vascular invasion by virus
- Frank vasculitis

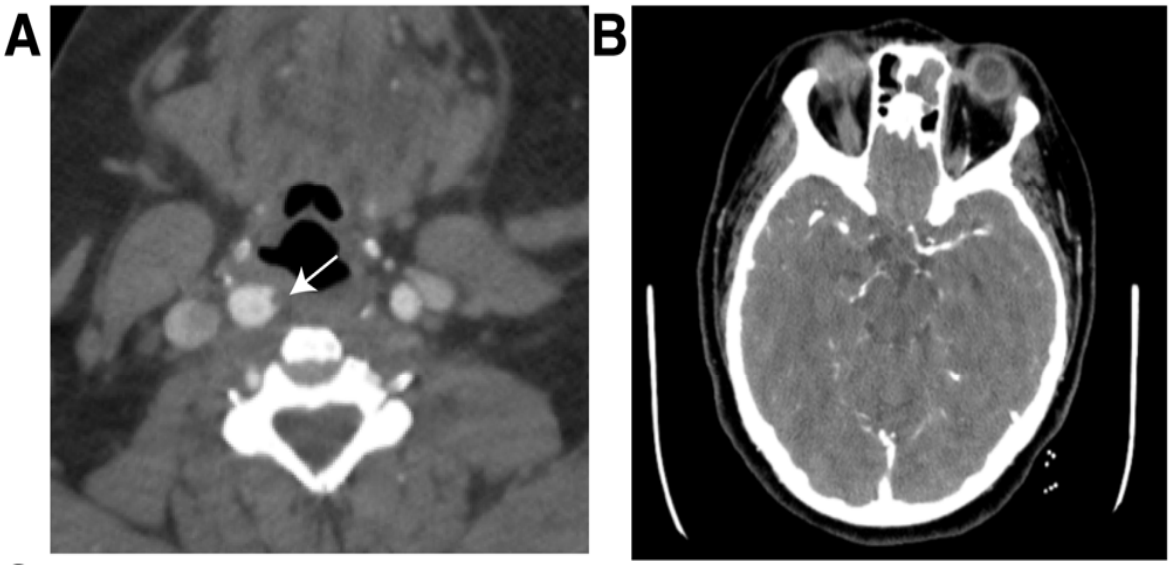
Endothelial activation elicits tissue factor release, endovascular recruitment of neutrophils releasing neutrophil extracellular traps (NETs) and von Willebrand factor (VWF) exocytosis from Weibel Palade bodies, leading to microvascular thrombosis



South K, et al . *Int J Stroke*. 2020;1747493020943815. doi:10.1177/1747493020943815

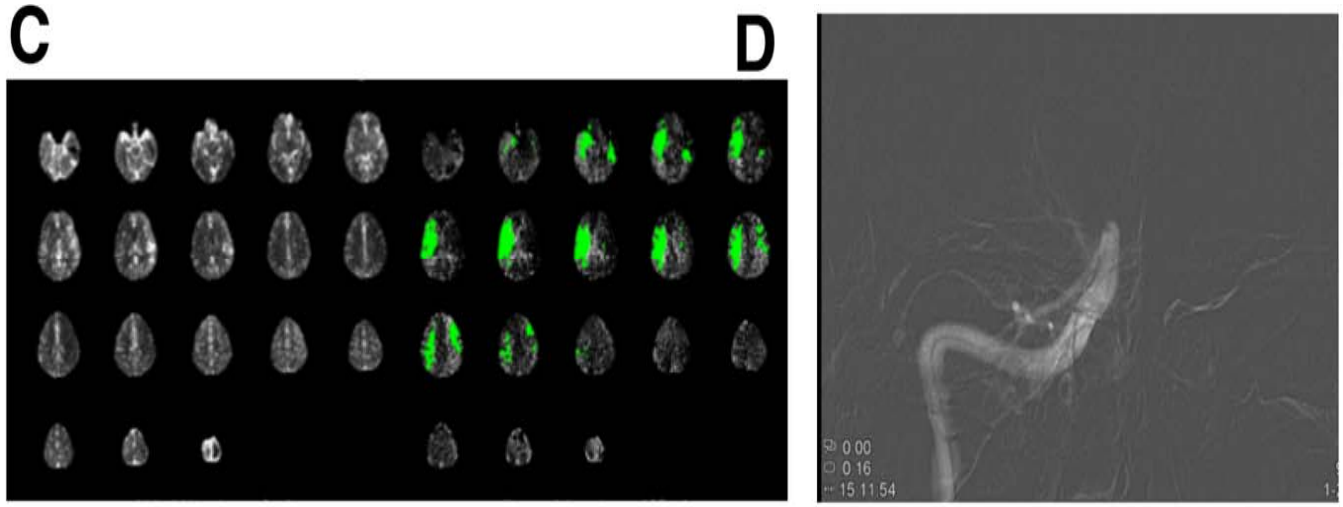
COVID and stroke case (1)

- A 37 year old Dominican woman with a history of morbid obesity, type 2 DM, HTN, and past preeclampsia presented with acute left hemiplegia.
- She had a 3-day history of cough and dyspnea, with mild fever, but outpatient PCR of the nasopharynx was negative for SARS-CoV-2.
- On examination, there was right gaze preference, mild left spatial neglect, left facial weakness, dysarthria, left arm plegia, left leg paresis, and intact sensation.
- Head CT showed a subtle dense right MCA sign.
- She received IV tPA.
- CT angiography showed a retropharyngeal course of the right ICA with retropharyngeal edema and filling defect in the medial aspect of the artery.
- Distal right carotid artery and middle cerebral artery stem were occluded, with distal collateralization.



COVID and stroke case (2)

CT perfusion study demonstrated no definite evidence of infarction, with a large perfusion defect in the right hemisphere. Angiography demonstrated occlusion of the right petrous carotid artery.

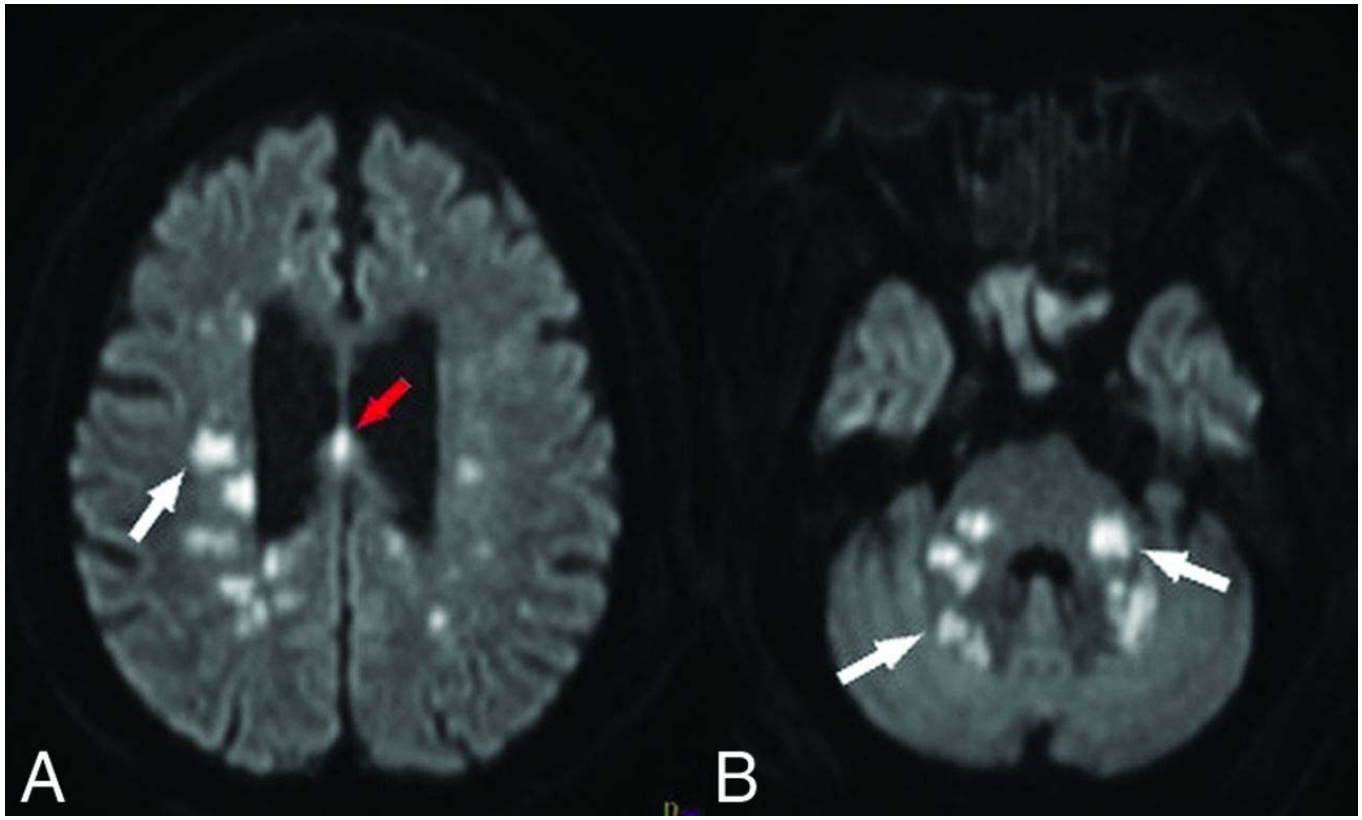


Thrombectomy was performed with good recanalization.
Repeat PCR testing for SARS-CoV-2 was positive. D-dimer and interleukin-6 levels were elevated, and fibrinogen levels were low. The patient had a good recovery and was discharged two days later.

COVID and stroke

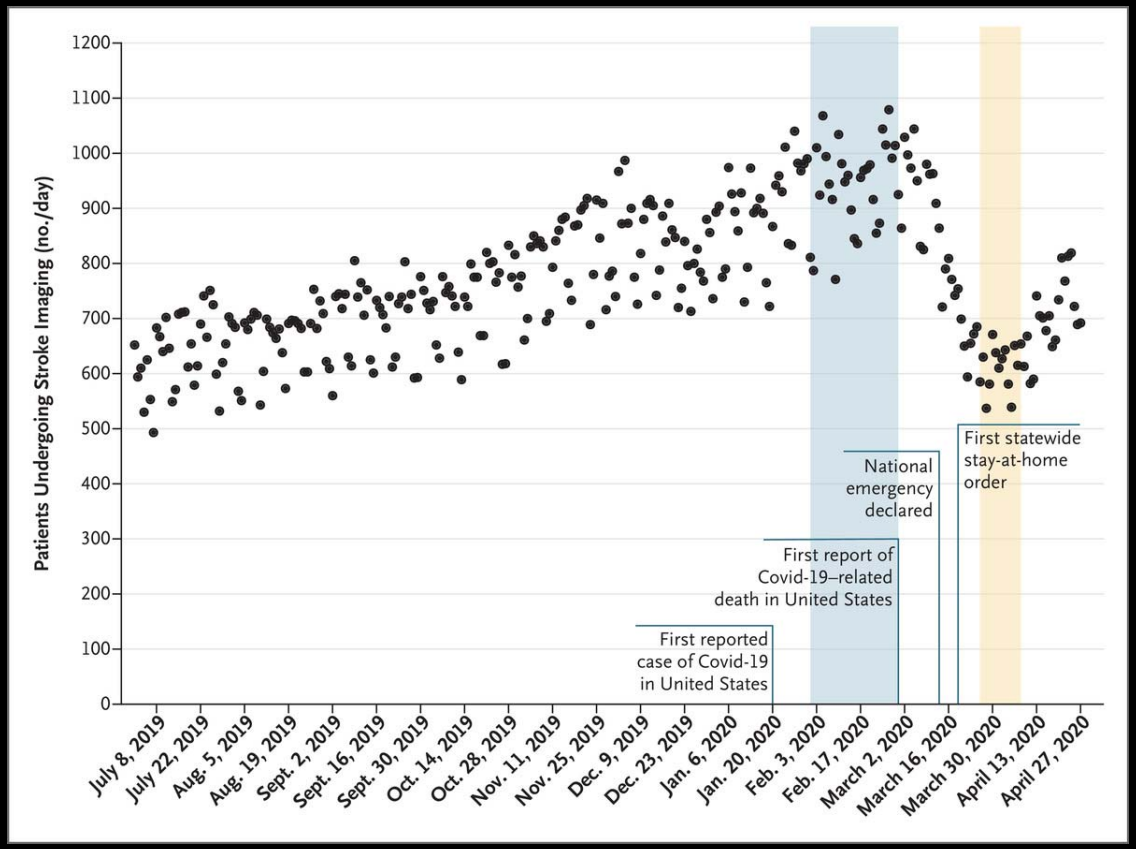
- Increased risk among Hispanics
- Increased risk of complications in those with cardiovascular risk factors
- Presentation with stroke
- Need for repeat testing to detect COVID
- Hypercoagulability
- “Thromboinflammation”

COVID “vasculitis”: diffuse deep white matter ischemic injuries



R. Hanafi et al. AJNR Am J Neuroradiol 2020;41:1384-1387

Daily Counts of Unique Patients Who Underwent Neuroimaging for Stroke in the United States, July 2019 through April 2020.



AP Kansagra et al. N Engl J Med 2020;383:400-401.

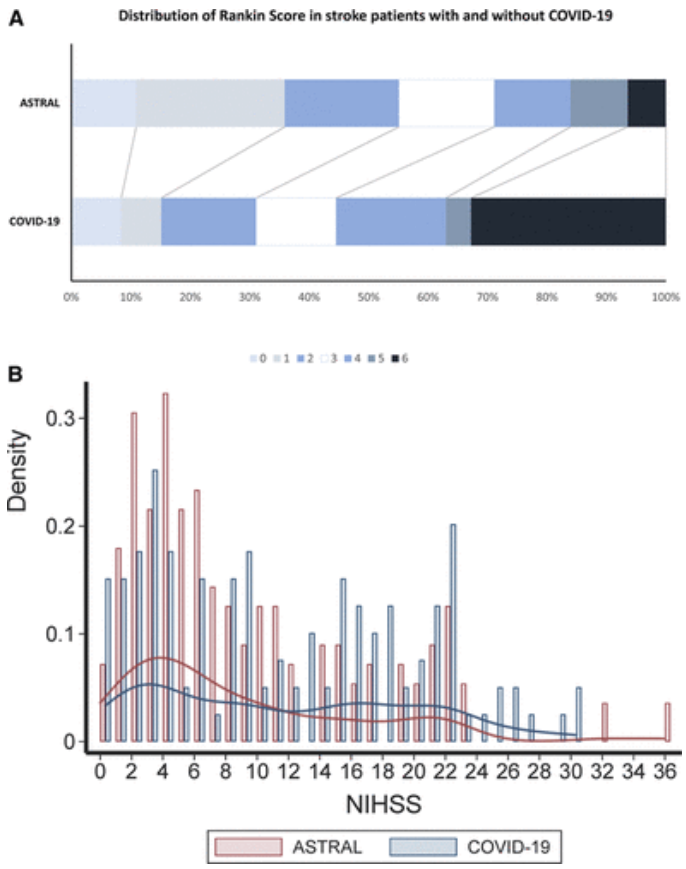
The NEW ENGLAND JOURNAL of MEDICINE

Fewer but more severe strokes

	Pre-COVID era Oct 2019-Feb 2020 [5 mos] n=275	COVID era Mar-Apr 2020 [6 wks] N=53	p
Patients per day			
Median (IQR)	2 (1-3)	1 (0-2)	<0.01
Mean	1.82 ± 1.38	1.13 ± 1.07	<0.01
Stroke severity (NIHSS)	5 (2-13)	8 (2-13)	NS
Mode of arrival			
Own vehicle	54%	30%	<0.01
EMS	45%	70%	<0.01
Time to IV tPA, min	39 (26-52)	39 (34-82)	0.46
LVO	21%	38%	0.01
Stroke mortality	7%	21%	<0.01

Siegler JE et al. J Stroke Cerebrovasc Dis 2020; 29(8):104953.

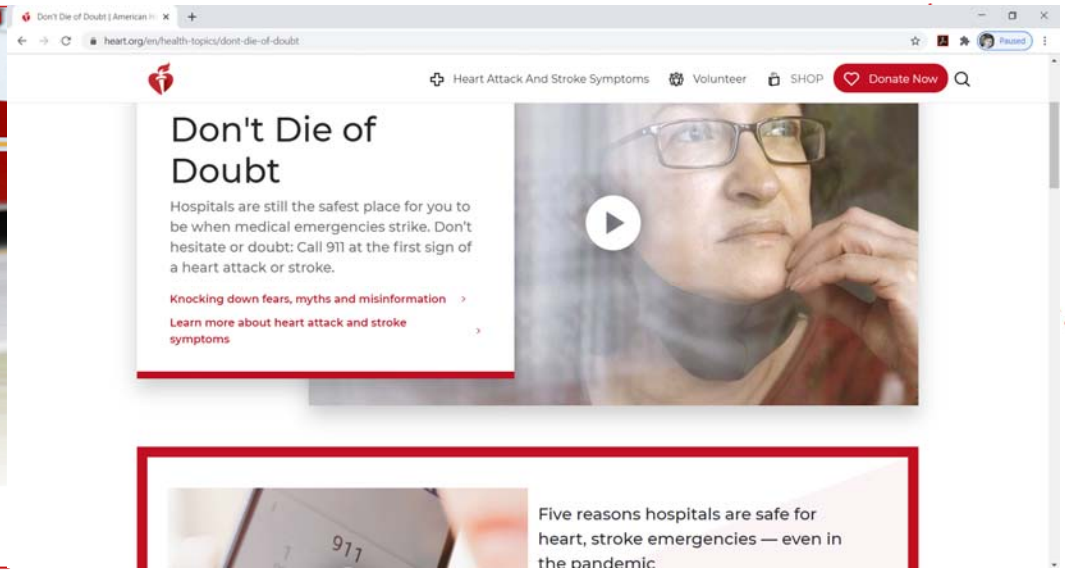
Strokes in patients with COVID are more severe and have higher mortality



Ntaios G et al. Stroke. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke, 51: e254-e258.

- Fear of going to hospital
- Not wanting to overwhelm healthcare system
- Lockdowns leading to less recognition of stroke symptoms
- Patients presenting with more severe strokes
- Less pollution and activity
- Can provide high quality care/meet quality measures

Don’t Die of Doubt!



American Heart Association.

ARCADIA Enrollment

- 1826 consented
- 481 randomized

Total subject Enrollment: 482 as of : 8/24/2020 9:37:31 PM

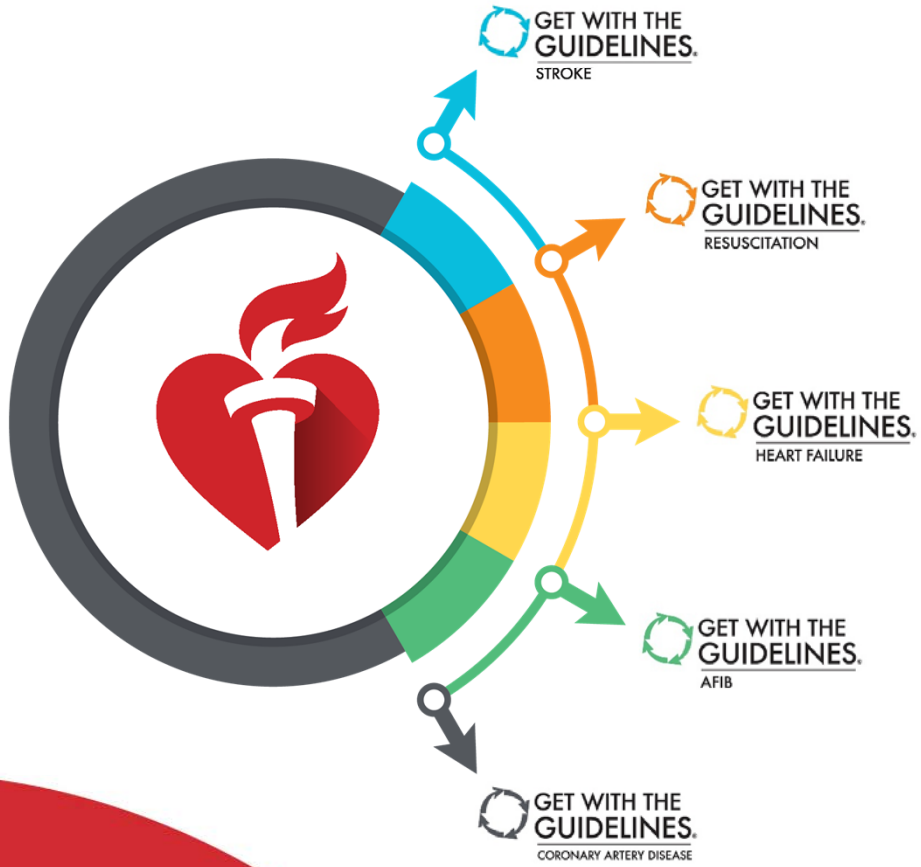
ARCADIA

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Recommendations to stroke patients/those at risk

- Wear a mask!
- Socially distance: (“Physical distancing, social solidarity”).
- Wash hands and items purchased before preparing.
- Wash hands frequently with soap and water, and do so for at least 20 seconds; use hand sanitizer as alternative.
- Keep extra refills of medications on hand in case of a prolonged period of unavailability of their pharmacy.
- If sick, stay at home, unless worsening symptoms (dyspnea) require hospital management.
- Call ahead to the hospital if going and wear a mask when going to the hospital.
- Follow the news, read WHO and CDC materials on line, and check with your local health authorities.
- Opportunity for coordinators to stay in touch with trial patients.

QUALITY IMPROVEMENT PROGRAMS



American Heart Association®
COVID-19 CVD Registry™
Powered by Get With The Guidelines®

- www.heart.org/covidregistry

American Heart Association®
COVID-19 CVD Registry™
Powered by Get With The Guidelines®

Stroke in COVID-19

- Stroke is rare in COVID (~1-3%)
- COVID may be common among stroke patients
- Patients can present with stroke
- Most are ischemic, though all subtypes occur
- Most ischemic stroke cryptogenic
- Strokes may occur in young patients without severe disease
- Stroke may be more common after COVID than after other respiratory infections (flu)
- Hypercoagulability and endothelial activation likely mechanisms
- Stroke admissions overall decreased during pandemic
- Mortality is high in COVID stroke
- Research needed!!

Thanks for your attention!

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